PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 67/307, 69/63, 69/708, 205/51

A1

(11) International Publication Number: **WO 97/00848**

(43) International Publication Date: 9 January 1997 (09.01.97)

(21) International Application Number: PCT/GB96/01355

(22) International Filing Date: 7 June 1996 (07.06.96)

(30) Priority Data:
9512546.4 20 June 1995 (20.06.95) GB

(71) Applicant *(for all designated States except US)*: BNFL FLUOROCHEMICALS LTD. [GB/GB]; B 619, Springfields Works, Salwick, Preston, Lancashire PR4 0XJ (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CHAMBERS, Richard, Dickinson [GB/GB]; University of Durham, Dept. of Chemistry, Science Laboratories, South Road, Durham DH1 3LE (GB). HUTCHINSON, John [GB/GB]; University of Durham, Dept. of Chemistry, Science Laboratories, South Road, Durham DH1 3LE (GB). THOMSON, Julie [GB/GB]; BNFL Fluorochemical Ltd., B 619, Springfields Work, Salwick, Preston, Lancashire PR4 0XJ (GB).

(74) Agent: McKERRACHER, Fiona, Kay; British Nuclear Fuels plc, IP & Patents Dept., Risley, Warrington, Cheshire WA3 6AS (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: A PROCESS FOR THE PREPARATION OF ESTERS

(57) Abstract

A process for the preparation of an ester, especially fluorinated esters $R_1O.OC\text{-}CFR_2\text{-}CO.OR_3$.$R_1$ and R_3 are each independently selected from alkyl, cycloalkyl and aryl. R_2 is selected from hydrogen, alkyl, cycloalkyl. The method includes the steps of covering a corresponding compound of formula 2: $R_1O.OC\text{-}CHR_2\text{-}CO.OR_3$ in the presence of a base, of salt of a compound of formula 2, into corresponding compound of formula 1 by the reaction of elemental fluorine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

A Process for the preparation of esters

The present invention relates to a process for the preparation of esters, in particular of fluorinated esters of dicarboxylic acids which comprise 2-fluoro- and 2,2-difluoro- malonic acid, and esters of 2-substituted-2-fluoro- malonic acids.

The use of elemental fluorine for the site specific fluorination of aliphatic compounds is rarely satisfactory due to the high reactivity of the element which leads to unspecific multiple substitution, carbon-carbon bond cleavage and oxidation. Because of the growing importance of fluorinated organic compounds in biochemical systems (R Filler and Y Kobayashi; Biochemical Aspects of Fluorine Chemistry; Elsevier Biomedical Press, New York, 1982.

J T Welch and S Eswarakrishnan; Fluorine in Bioorganic Chemistry; John Wiley, New York, 1991) in recent years considerable effort has been devoted to finding ways of introducing fluorine into specific sites within molecules. Such molecules are valuable building blocks for the synthesis of biologically active compounds which have more complex structures. In this context, the preparation of fluoromalonic esters and difluoromalonic esters has aroused much interest since these compounds are useful intermediates in the preparation of bioactive molecules (T Tsushima, K Kawada, O Shiratori and N Uchida; Heterocycles, 1985, 1, 45). Hitherto, these compounds have been prepared by treating the alkali metal salts of malonic esters with an "electrophilic fluorinating agent" such as perchloryl fluoride (C E Inman, R E Oersterling and E A Tyczkowski; J Amer. Chem. Soc., 1958, 80, 6533),

N-fluoro-N-sulphonamides (W E Barnette; J Amer. Chem. Soc., 1984, 106, 453), N-fluoro-2-pyridone (S T Purrington and W A Jones; J Org. Chem., 1983, 48, 761), N-fluoro-benzenesuphonimides (E Differding and H Ofner; Synlett., 1991, 187), N-Fluoro-pyridinium salts (with or without the addition of a Lewis acid) (T Umemoto, S Fukami, G Tomizawa, K K Harasawa, K Kawada and K Tomita; J. Amer. Chem. Soc., 1990, 112, 8575), 1-alkyl-4-fluoro-1,4-diazabicyclo[2,2,2,]octane salts (G A Lal; J. Org. Chem., 1993, 58, 2791. R E Banks, N J Lawrence and A L popplewell; J. Chem. Soc., Chem. Commun., 1994, 343), N-fluoro-bis(perfluoroalkyl)sulphonimides (Z. Xu, D. D. Desmarteau and Y Gotoh; J. Chem. Soc., Chem. Commun., 1991, 179. Z. Xu, D D Desmarteau and Y Gotoh; J. Fluorine Chem., 1992, 58, 71. G Resnati and D D Desmarteau; J. Org. Chem., 1991, 56, 4925), perfluoropiperidine (R E Banks and G E Williamson; Chem. Ind. (London), 1964, 1864) and acetyl hypofluorite (O Lerman and S Rozen; J. Org., Chem., 1983, 48, 724).

Although the treatment of alkali metal salts of malonic esters with electrophilic fluorinating agents can sometimes give high yields of the required mono- or di-fluorinated products, some of these reagents decompose fairly quickly, and the compounds from which they are made are often expensive or difficult to obtain.

Other methods for making esters of 2-fluoro- and 2,2,-difluoro- malonic acids are less direct. They are frequently inefficient, involve several steps in their synthesis or require starting materials which are expensive or difficult to obtain.

Thus, the prior art methods of preparing malonic esters are not satisfactory.

Surprisingly, we have now found a convenient and efficient process for the preparation of esters of 2-fluoro- and 2,2-difluoro- malonic acids which involves the use of elemental fluorine.

According to the present invention there is provided a process for the preparation of an ester having a formula 1:

$R_1O.OC-CFR_2-CO.OR_3$

formula 1

which includes the steps of converting the corresponding compound of formula 2 as follows

$R_1O.OC-CHR_2-CO.OR_3$

formula 2

in the presence of a base, or a salt of a compound of formula 2, into the corresponding fluorinated compound of formula 1 by reaction with elemental fluorine.

In formulae 1 and 2, R_1 and R_3 are each independently selected from alkyl, cycloalkyl and aryl.

In formulae 1 and 2, R_2 is selected from hydrogen, alkyl, cyclo-alkyl, preferably C_{1-6} alkyl, nitro, cyano, halogen, alkoxy, acetamido, alkoxycarbonyl, aryloxycarbonyl and aryl.

Where R_2 is formula 2 is hydrogen, R_2 in formula 1 may be fluorine. Thus, substitution by fluorine may take place at both available hydrogen atoms attached to the internal carbon atom of the molecule.

The ester of formula 2 may be added to a base before fluorination. For example, the ester of formula 2 may be added to an inorganic base such as an alkali metal hydride or alkoxide which before fluorination converts the ester into a salt in one of the ways well known to those skilled in the art.

Thus, the salt which takes part in the fluorination may have formula 3 as follows:

$R_1O.OC-CMR_2-CO.OR_3$

formula 3

where M is a suitable cation, eg an alkali metal, and R_1 to R_3 are as defined above.

Alternatively, a base which is not employed to convert the ester of formula 2 into a salt may be employed to promote fluorination. Such a base may be added to the reacting ester before or during addition of fluorine. Suitable bases include alkali metal halides, eg fluorides, eg sodium, potassium or caesium fluoride, organic bases such as pyridine or substituted pyridines, organic amines such as trialkylamines or Proton Sponge ®.

The process according to the present invention may be carried out by passing fluorine gas into a suitably inert liquid containing the ester and base or the salt. A suitably inert organic for this process solvent would be acetonitrile. The reaction may be carried out in a vessel in which the said liquid is present or alternatively a flow stream of the liquid may be contacted with a gaseous flow of fluorine in countercurrent fashion.

The process may be carried out at a temperature of from -45°C to 80°C, preferably at a temperature from -20°C to 30°C and especially at a temperature from -10°C to 15°C.

The fluorine gas employed in the process according to the present invention is preferably diluted before use by mixing with an inert gas such as nitrogen or helium. The concentration of fluorine is preferably from 1% to 50% by volume, more preferably from 2% to 25% and especially from 5% to 15%.

The ratio of fluorine to ester of formula 2 or its salt may be varied within wide limits although it is preferred that the molar ratio of fluorine to ester or salt is from 0.5:1 to 6:1, and especially from 0.8:1 to 3:1. Use of a higher ratio of fluorine to ester or salt ensures that two fluorine atoms are introduced into the molecule where required.

When fluorination is complete the fluorinated products may be isolated by purging the reaction mixture with nitrogen to remove any residual fluorine gas followed by a suitable separation process such as distillation.

The method according to the present invention surprisingly and beneficially offers a simple and convenient route to the preparation of fluorinated esters of dicarboxylic acids such as malonic acids directly from the parent unfluorinated ester using elemental fluorine.

For example, the present process provides an inexpensive and convenient synthetic route to 2-fluoro- and 2,2-difluoro-esters of malonic acid.

The method according to the present invention is further illustrated by way of example only with reference to the following Examples:

Example 1 Preparation of diethyl 2-fluoro- and diethyl 2,2-difluoro-malonates

A solution of diethyl malonate (2.0 gm, 12.5 mmol) in dry acetronitrile (10 ml) was added over 30 min. to a suspension of degreased sodium hydride (0.3gm., 12.5 mmol.) in dry acetonitrile (50 ml) at room temperature. Through the cooled (ca. -15°C) white suspension of the sodium derivative was bubbled fluorine (25 mmol.) diluted to 10% in nitrogen over a period of 1 hour during which time the temperature was maintained between -20°C and -15°C. After this treatment, the reaction vessel was purged with nitrogen and allowed to warm to room temperature (20°C). The colourless solution was filtered and most of the solvent removed by distillation to give 1.9 gm of a pale yellow liquid. Short path length, reduced pressure distillation of 1.6gm of this material yielded 1.45gm of a mixture of acetonitrile, unreacted diethyl malonate, diethyl fluoromalonate ([$d_F(CDCl_3)$ -195.6ppm, (d) 50.3Hz., m/z 178], and diethyl difluoromalonate [$d_F(CDCl_3)$ -112.7ppm, (s), m/z 196]. The conversion was ca. 70% and the yields of the monofluoro- and difluoro- compounds were 37% and 24% respectively.

Example 2 Preparation of diethyl 2-fluoro- and diethyl 2,2-difluoro- malonates

A reaction similar to that described in Example 1 was carried out in which 25 mmol. diethyl malonate was treated successively with 56 mmol. sodium hydride and 75 mmol.

fluorine. The conversion was 94% and the yields of diethyl 2-fluoro- and diethyl 2,2-difluoro- malonates were 14% and 37% respectively.

Example 3 Reaction of Diethyl malonate and fluorine without base

To demonstrate the importance of treating the diester with base, fluorine (50 mmol, 10% in nitrogen) was passed through a solution of diethyl malonate (4gm, 25 mmol) in acetonitrile over 1 hour 30 min with no base present. After purging with nitrogen, the nmr spectrum of the reaction product showed the complete absence of any fluorinated derivatives of diethyl malonate.

Example 4 Preparation of diethyl 2-fluoro-2-methylmalonate

By a similar method to that described in Example 1, diethyl methylmalonate (4.35 gm, 25 mmol) was dissolved in acetonitrile (10 ml) and treated successively with degreased sodium hydride (0.6 gm, 25 mmol), 1 eq) in dry acetonitrile (40 ml) and fluorine (1.9 gm, 50 mmol, 2 eqs) (10% in nitrogen). After this treatment, the reaction mixture was purged with nitrogen, allowed to warm to room temperature (20°C) and filtered. Most of the solvent was removed by distillation to give a pale yellow liquid (4.7 gm). Short path length reduced pressure distillation of 3.6 gm of this material gave a mixture (2.8 gm) of acetonitrile starting material and diethyl 2-fluoro-2-methylmalonate [d_F ($CDCl_3$)-158.0 ppm, (q), 22.2 Hz; m/z (CI, NH_3) 210 (100%)]. Conversion was 74% and the yield of diethyl 2-fluoro-2-methylmalonate was 60%.

Example 5 Preparation of diethyl 2-fluoro-2-methylmalonate

Under an atmosphere of nitrogen, diethylmethylmalonate (4.35 gm), 25 mmol) dissolved in acetonitrile (10 ml) was added to a suspension of sodium ethoxide (96%, 1.8 gm, 25 mmol) in acetonitrile (40 ml). The reaction mixture was heated to about 45°C for 20 mins and then cooled to -20°C at which temperature fluorine (50 mmol) diluted with nitrogen to 10% was bubbled through the reaction mixture over a period of 1 hour 40 mins. After this treatment, the reaction mixture was purged with nitrogen, allowed to warm to room temperature (20°C) and filtered. Most of the solvent was removed from the filtrate by distillation to yield a pale yellow liquid (5.1 gm). Short path length, reduced pressure distillation of 4.7 gm of this material afforded of a mixture (4.1 gm) of solvent, starting material and 2-fluoro-2-methylmalonate. Conversion was 40% and the yield of 2-fluoro-2-methylmalonate was 60%.

Example 6 Preparation of diethyl 2-butyl-2-fluoromalonate

By a similar method to that described in Example 1, diethyl 2-butylmalonate (5.40 gm, 25 mmol) was dissolved in acetonitrile (10 ml) and added to a suspension of degreased sodium hydride (0.75 gm, 32.25 mmol) in acetonitrile (40 ml) and treated with fluorine (ca 2.2 gm, 57 mmol, 2.3 eqs) (10% nitrogen). After this treatment, the reaction mixture was purged with nitrogen, allowed to warm to room temperature and filtered. Most of the solvent was removed to give a yellow liquid (6.2 gm). Short path length, reduced pressure distillation of 4.8 gm

of this material gave 4.2 gm of a mixture of acetonitrile, starting material and diethyl 2-butyl-2-fluoromalonate [d_F ($CDCl_3$)-167.7 ppm (t), ca 22.8 Hz); m/z (CI, NH_3) 252 (100%, 234 + 18)]. A conversion of 65% was obtained and the yield of diethyl 2-butyl-2-fluoromalonate was 70%.

Example 7 Preparation of dimethyl 2-fluoro-2-methoxymalonate

By a similar method to that described in Example 1, dimethyl-2-methoxymalonate (4.05 gm, 25 mmol) was dissolved in acetonitrile (10 ml) and added to a suspension of degreased sodium hydride (0.75 gm, 31.25 mmol 1.25 eqs) in acetonitrile (40 ml). The mixture was heated to a temperature of from 40°C to 45°C for about 1 hour. After cooling, fluorine (ca 2.7 gm, 71.42 mmol, 2.86 eqs) (10% in nitrogen) was bubbled through the suspension at a temperature of about -10°C over a period of 2 hr 15 min. After this treatment, the reaction mixture was purged with nitrogen, allowed to warm to room temperature and filtered. Most of the solvent was removed by distillation to give a pale yellow liquid (5.3 gm). Short path length, reduced pressure distillation of 4.2 gm of this material gave 3.6 gm of a mixture of solvent, starting material and dimethyl 2-fluoro-2-methoxymalonate [d_F ($CDCl_3$)-124.4(s); d_H ($CDCl_3$) 3.90 ppm (s, CO_2Me); 3.57 (s, Ome); m/z (CI, NH_3) 198]. Conversion was 75% and the yield of dimethyl 2-fluoro-2-methoxymalonate was 50%.

Example 8 Preparation of diethyl 2-chloro-2-fluoromalonate

By a similar method to that described in Example 1, diethyl 2-chloromalonate (4.86 gm, 25 mmol) was dissolved

in acetonitrile (10 ml) and added to a suspension of degreased sodium hydride (0.75 gm, 32.25 mmol, 1.25 eqs) in acetonitrile (40 ml) and treated with fluorine (ca 1.9 gm, 50 mmol, 2 eqs) (10% in nitrogen). After this treatment, the reaction mixture was purged with nitrogen, allowed to warm to room temperature and filtered. Most of the solvent was removed by distillation to give a pale yellow liquid (5 gm). Short path length, reduced pressure distillation of 4.1 gm of this material gave 2.2 gm of a mixture of acetonitrile, starting material and diethyl 1-chloro-1-fluoromalonate ($d_F(CDCl_3)$-120.8 ppm; m/z (CI, NH_3) 230 (13.3%, 212 + 18), 196 (100%)]. Conversion was 97% and the yield of diethyl 1-chloro-1-fluoromalonate was 40%.

Example 9 Preparation of diethyl 2-fluoro-2-nitromalonate

By a similar method to that described in Example 1, diethyl 2-nitromalonate (5.13 gm, 25 mmol) was dissolved in acetonitrile (10 ml) and added to a suspension of degreased sodium hydride (0.75 gm, 32.25 mmol, 1.25 eqs) in acetonitrile (40 ml) and treated with fluorine (ca 1.90 gm, 50 mmol, 2 eqs) (10% nitrogen). After this treatment, the reaction mixture was purged with nitrogen, allowed to warm to room temperature and filtered. Most of the solvent was removed by distillation to give a pale yellow liquid (5 gm). Short path length, reduced pressure distillation of 4gm of this material gave 3.5gm of a mixture of acetonitrile and diethyl 2-fluoro-2-nitromalonate [d_F ($CDCl_3$) -127.3 ppm, (s); m/z (CI, NH_3) 241 (4.4%, 223 + 18); 196 (100%). The yield of diethyl 2-

fluoro-2-nitromalonate was 73% for a quantitative conversion.

Example 10 Preparation of diethyl 2-fluoro-2-nitromalonate

In a manner similar to that described in Example 5, diethyl 2-nitromalonate (5.1 gm, 25 mmol) dissolved in acetonitrile (10 ml) was added to a suspension of sodium ethoxide (96%, 1.8 gm, 25 mmol) in acetonitrile (40 ml) over about 7 min and stood for a further 10 min to give a yellow solution. The reaction mixture was cooled to a temperature of -20°C and fluorine (50 mmol) diluted with nitrogen to 10% was bubbled through it over a period of 2 hours. After this treatment, the reaction mixture was allowed to warm to room temperature, filtered, and most of the solvent was removed from the filtrate by distillation to yield a pale yellow liquid (6.9gm). Short path length, reduced pressure distillation of 4.7gm of this material afforded 4.3gm of a mixture which was analysed by gc and nmr. Conversion was 77% and the yield of 2-fluoro-2-nitromalonate was 90%.

Example 11 Preparation of diethyl 2-fluoro-2-nitromalonate

Fluorine (57 mmol) diluted with nitrogen to 10% was passed through a slurry of potassium fluoride (5.8gm 100 mmol) in a solution of diethyl 2-nitromalonate(5.1 gm, 25 mmol) in actetonitrile (50 ml) at a temperature of -15°C over a period of 2 hours. After this treatment, the reaction mixture was purged with nitrogen, allowed to warm to room temperature and filtered. Most of the solvent was removed by distillation to give 6.2gm of a pale yellow

liquid. Short path length, reduced pressure distillation of 5.6gm of this material gave 5.2gm distillate which was analysed by gc and nmr. Conversion was 70% and the yield of diethyl 2-fluoro-2-nitromalonate was 85%.

CLAIMS

1. A process for the preparation of an ester of formula 1:

$R_1O.OC-CFR_2-CO.OR_3$

formula 1

wherein:

R_1 and R_3 are each independently selected from alkyl, cycloalkyl and aryl.

R_2 is selected from hydrogen, alkyl, cycloalkyl, preferably C_{1-6} alkyl, nitro, cyano, halogen, alkoxy, acetamido, alkoxycarbonyl, aryloxycarbonyl, and aryl; the method comprising the steps of converting a corresponding compound of formula 2:

$R_1O.OC-CHR_2-CO.OR_3$

formula 2

in the presence of a base, or a salt of a compound of formula 2, into the corresponding compound of formula 1 by reaction with elemental fluorine.

2. A process as in Claim 1 and wherein a compound of formula 2 is converted into a salt prior to fluorination of the salt with elemental fluorine.

3. A process as in Claim 1 and wherein a compound of formula 2 is present with a base which does not substantially form a salt therewith during the fluorinations of the compound of formula 2 with elemental fluorine.

4. A process as in Claim 1, 2 or 3 and wherein the fluorine is passed into a liquid containing the compound of formula 2 or salt.

5. A process as in Claim 4 and wherein the fluorine is passed into a liquid containing a compound of formula 2, the liquid comprising an inert organic solvent which also includes the base.

6. A process as in any one of Claims 4 to 5 and wherein the fluorine is diluted with an inert gas prior to being passed into the said liquid.

7. A process as in Claim 1 and wherein the ester of formula 1 has terminal groups R_1 and R_5 which are independently n-alkyl groups having from 1 to 4 carbon atoms.

8. A process substantially as herein described with reference to the specific Examples.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 96/01355

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C67/307 C07C69/63 C07C69/708 C07C205/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,95 14646 (BNFL FLUOROCHEMICALS LTD) 1 June 1995 see page 3, paragraph 4 - page 4, paragraph 2 see page 4, paragraph 5 - page 5, paragraph 3 see page 11 - page 12; claims ---	1
A	WO,A,94 10120 (DAIKIN INDUSTRIES LTD) 11 May 1994 * ABSTRACT * ---	1
A,P	& EP,A,0 667 332 (DAIKIN INDUSTRIES LTD) 18 August 1995 see page 7, line 54 - page 8, line 27 see page 10, line 25 - line 35 see page 13; example 22 see page 17 - page 18; examples 5,6 see page 19; claims 1-3 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1996	02. 09. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Kinzinger, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 96/01355

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9514646	01-06-95	NONE	
WO-A-9410120	11-05-94	EP-A- 0667332	16-08-95